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## Body surface area as a prognostic marker in chronic heart failure patients: results from the Heart Failure Registry of the Heart Failure Association of the European Society of Cardiology

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### Abstract

**Aims.** The ‘obesity paradox’ is consistently observed in patients with heart failure (HF). We investigated the relationship of body surface area (BSA) to mortality and hospitalizations in patients with chronic HF.

**Methods and results.** Data from the outpatient cohort of the observational, prospective, Heart Failure Long-Term Registry of the Heart Failure Association of the European Society of Cardiology was analysed in order to evaluate the prognostic significance of BSA in chronic HF. A total of 9104 chronic HF patients (age  $64.8 \pm 13.4$  years; 71.6% males) were enrolled. Mortality during 1-year follow-up was observed in 718 of 8875 (8.1%) patients. A progressive, inverse relationship between all-cause mortality and BSA levels was observed; the adjusted hazard ratio (HR) for 1-year mortality was 1.823 [95% confidence interval (CI) 1.398–2.376],  $P < 0.001$  for the lowest quartile of BSA  $<1.78 \text{ m}^2$ , and 1.255, 95% CI 1.000–1.576,  $P = 0.05$  for the middle two quartiles ( $1.78 \leq \text{BSA} \leq 2.07 \text{ m}^2$ ), compared with the highest quartile ( $\text{BSA} > 2.07 \text{ m}^2$ ). For each increase of  $0.1 \text{ m}^2$  in BSA, an adjusted HR of 0.908 (95% CI 0.870–0.948),  $P < 0.001$  for mortality was calculated. HF hospitalizations were not associated with BSA subgroup distribution. In both genders, subjects within the lowest BSA quartile (males  $<1.84 \text{ m}^2$  and females  $<1.64 \text{ m}^2$ ) had significantly higher mortality rates during follow-up (log-rank  $P < 0.0001$ ). However, the stepwise association with mortality was more distinct in males.

**Conclusions.** Total and cardiovascular mortality, but not HF hospitalizations was inversely associated with BSA levels in chronic HF patients. BSA may serve as a prognostic indicator for adverse outcome in HF patients.

### Keywords

Heart failure; Body surface area; Obesity; Prognosis

## Introduction

Obesity is an established risk factor for the development of cardiovascular diseases including heart failure (HF).<sup>1</sup> However, numerous studies have demonstrated survival benefit of overweight and mildly obese HF subjects compared with leaner individuals with HF, and the unfavourable prognostic significance of loss of body weight.<sup>2-11</sup> This phenomenon of reverse epidemiology was termed the 'obesity paradox', and is now well documented in chronic HF.

Mechanisms explaining the obesity paradox in HF are not clearly defined, and include the effects of cardiac cachexia, catabolic state, and muscle wasting in lean HF subjects, in contrast to greater metabolic reserve and increased muscle mass and strength in overweight and obese HF individuals.<sup>12, 13</sup> It may also be that obese patients present earlier in their disease course due to greater functional impairment and are therefore treated earlier. Furthermore, it is possible that confounding factors such as disease severity, lower incidence of smoking, and younger age may account for the inverse relationship between obesity and mortality seen in HF cohorts.<sup>14, 15</sup> Nevertheless, it is still debated whether there is an intrinsic association between obesity and mortality in HF subjects, or whether the obesity paradox is confounded by other uncontrolled factors contributing to its existence.<sup>16-18</sup>

Body mass index (BMI) is the most common anthropometric parameter used in studies assessing obesity in patients with chronic HF, due to its widespread acceptance and ease of use. Less commonly, measures of body composition such as increased waist circumference and estimates of body fat were also shown to be associated with improved outcomes in HF.<sup>19, 20</sup> Though commonly used, BMI may not be a reliable method to assess the distribution and degree of adiposity or a good way to correct weight for height. Body surface area (BSA), a method for describing body size, is commonly used as a biometric unit to adjust mass and volume and for indexing physiological parameters associated with cardiovascular disease, and may correlate more closely with prognosis in HF.<sup>21</sup> Although BSA is commonly used as a way to 'index' haemodynamic parameters, its prognostic significance in HF has not been robustly studied.

The objective of the current study was to examine the prognostic significance of BSA in predicting survival and hospitalizations in a large population of chronic HF patients.

## Methods

### *Study design*

The chronic HF cohort of the Heart Failure Long-Term Registry comprised the study population.<sup>22</sup> This registry is a prospective, multicentre, observational study of patients presenting to 211 Cardiology centres of 21 European and Mediterranean countries. Patients were enrolled in the registry from outpatient HF clinics as well as from hospital admissions for acute, pre-existing, or new-onset HF during the enrolment period, on a 'one day per week' basis for 12 consecutive months in each participating country.

Included in the present study were all recruited outpatients with chronic HF diagnosed according to the clinical judgement of the responsible cardiologist at the participating centres. The cohort of inpatients admitted to hospitals for acute HF was not part of the present analysis. There were no specific exclusion criteria, with the exception that all patients had to be aged over 18 years. The survey was approved by each local Institutional Review Board according to the rules of each participating country. No data were collected before detailed information was provided to the patient, and a signed, informed consent was obtained.

Baseline demographics, clinical characteristics, and co-morbidities were recorded in all patients, including drug treatment and laboratory blood tests at study entry. One-year outcome data were collected in each participating site, including overall and cardiovascular mortality, as well as HF hospitalizations during the follow-up period.

All subjects had documented BSA measurements carried out at their initial visit to the outpatient HF clinic. BSA was calculated according to the Mosteller formula  $[\text{weight (kg)} \times \text{height (cm)} / 3600]^{1/2}$ .<sup>23</sup> Mosteller's formula is recommended as an accurate measure to estimate BSA, and is commonly used due to its simplicity and applicability in both clinical and laboratory medicine.<sup>24</sup>

### *Statistical analysis*

Univariate analysis was applied to both continuous and categorical variables. Continuous variables were reported as mean  $\pm$  SD or as median and interquartile range (IQR). Among-group comparisons were made using a non-parametric test (Kruskal–Wallis test). Categorical variables were reported as percentages. Intergroup comparisons were made using a  $\chi^2$  test or a Fisher's exact test if any expected cell count was less than five. In order to assess the prognostic value of BSA, the patients were categorized into three groups based on quartiles of BSA [ $<Q1$  ( $1.78 \text{ m}^2$ );  $Q1$ – $Q3$  ( $1.78$ – $2.07 \text{ m}^2$ );  $>Q3$  ( $2.07 \text{ m}^2$ )]. Additional analysis was performed for BSA as a continuous variable.

Multivariable analysis was performed using the Cox proportional hazards analysis. All variables significant in a univariate analysis were inserted in the model. A stepwise regression model was performed, where BSA was the fixed variable. Hazard ratios (HRs) for overall 1-year mortality were calculated for the subgroups of BSA and additional significant covariables, with 95% confidence intervals (CIs). Adjustment for age and gender was also performed in a separate model in order to assess the effect of age and gender on the association between BSA and mortality.

Survival curves were plotted by the Kaplan–Meier method using the log-rank test for assessing the significance of the differences in survival between BSA subgroups. As BSA values are commonly lower in females than in males, additional plots were made according to the specific quartiles of each gender.

The results were considered statistically significant when the *P*-value was  $<0.05$ . Analyses were performed with SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

## **Results**

Included in the study were 9104 participants of the outpatient cohort of the ESC Heart Failure Long-Term Registry. The baseline characteristics of the patients included in the study are presented in *Table 1*. Mean age of the study population was  $64.8 \pm 13.4$  years, and there was predominance of men (71.6%). Only 25.7% were in NYHA functional class III–IV. An LVEF of  $\leq 45\%$  was documented in 77.0% of the patients. Ischaemic heart disease as a primary aetiology was present in 42.8% and diabetes mellitus in 31.3%.

**Table 1.** Baseline characteristics of patients according to body surface area (m<sup>2</sup>)

	All (n = 9104)	<1.78 (n = 2226)	1.78–2.07 (n = 4652)	>2.07 (n = 2226)	P-value
Age (years)	64.8 ± 13.4	67.6 ± 15.1	65.4 ± 12.8	60.6 ± 11.6	<0.001
Female gender	2584/9104 (28.4%)	1310/2226 (58.9%)	1074/4652 (23.1%)	200/2226 (9.0%)	<0.001
BMI (kg/m <sup>2</sup> )	28.1 ± 5.1	23.8 ± 3.3	27.8 ± 3.6	33.0 ± 5.1	<0.001
SBP (mmHg)	124.4 ± 21.0	120.8 ± 21.0	124.4 ± 20.7	128.1 ± 20.8	<0.001
HR (b.p.m.)	73.2 ± 15.7	72.6 ± 15.3	72.6 ± 15.4	74.9 ± 16.5	<0.001
EF (%)	37.1 ± 13.6	38.2 ± 15.1	37.0 ± 13.4	36.1 ± 12.5	0.008
EF (%) median (IQR)	35 (27–45)	35 (27–49)	35 (28–45)	35 (27–45)	
NYHA III–IV	2343/9102 (25.7%)	599/2226 (26.9%)	1142/4651 (24.6%)	602/2225 (27.1%)	0.030
Sound 3	547/9060 (6.0%)	126/2216 (5.7%)	281/4633 (6.1%)	140/2211 (6.3%)	0.661
Mitral regurgitation	2415/9079 (26.6%)	619/2220 (27.9%)	1233/4640 (26.6%)	563/2219 (25.4%)	0.166
Aortic stenosis	370/9077 (4.1%)	123/2219 (5.5%)	181/4640 (3.9%)	66/2218 (3.0%)	<0.001
HF history with previous hospitalization	3767/9043 (41.7%)	954/2219 (43.0%)	1904/4611 (41.3%)	909/2213 (41.1%)	0.335
Ischaemic heart disease	3900/9104 (42.8%)	803/2226 (36.1%)	2139/4652 (46.0%)	958/2226 (43.0%)	<0.001
Atrial fibrillation	3370/9104 (37.0%)	780/2226 (35.0%)	1709/4652 (36.7%)	881/2226 (39.6%)	0.006
Diabetes mellitus	2853/9104 (31.3%)	511/2226 (23.0%)	1486/4652 (31.9%)	856/2226 (38.5%)	<0.001
PAD	1100/9081 (12.1%)	273/2219 (12.3%)	583/4640 (12.6%)	244/2222 (11.0%)	0.162
Hypertension	5357/9098 (58.9%)	1138/2223 (51.2%)	2756/4649 (59.3%)	1463/2226 (65.7%)	<0.001
COPD	1272/9089 (14.0%)	295/2222 (13.3%)	632/4643 (13.6%)	345/2224 (15.5%)	0.056
Prior stroke/TIA	844/9098 (9.3%)	193/2224 (8.7%)	479/4648 (10.3%)	172/2226 (7.7%)	0.001
Renal dysfunction	1746/9095 (19.2%)	453/2225 (20.4%)	905/4645 (19.5%)	388/2225 (17.4%)	0.036
Hepatic dysfunction	320/9090 (3.5%)	70/2222 (3.2%)	167/4643 (3.6%)	83/2225 (3.7%)	0.531
Depression	666/9075 (7.3%)	202/2215 (9.1%)	348/4637 (7.5%)	116/2223 (5.2%)	<0.001
CRT implantation	1187/9020 (13.2%)	285/2214 (12.9%)	611/4606 (13.3%)	291/2200 (13.2%)	0.899
ICD implantation	2204/9028 (24.4%)	454/2216 (20.5%)	1165/4610 (25.3%)	585/2202 (26.6%)	<0.001

BMI, body mass index; BSA, body surface area; HF, heart failure; HR, heart rate; ICD, implantable cardioverter defibrillator; IQR, interquartile range; PAD, peripheral artery disease; SBP, systolic blood pressure; TIA, transient ischaemic attack.

Study patients were divided according to quartiles of BSA [<1.78 m<sup>2</sup> (Q1); (1.78–2.07 m<sup>2</sup>) (Q1–Q3); >2.07 m<sup>2</sup> (Q3)]. Higher BSA subgroups were significantly associated with younger age and predominance of male gender. In addition, higher BSA was associated with greater prevalence of co-morbidities, including obesity, hypertension, diabetes mellitus, and AF. The rate of depression was inversely related to BSA.

Drug treatment and laboratory blood tests during outpatient visits according to BSA subgroups are presented in *Table 2*. Almost 90% of patients were treated with ACE inhibitors or ARBs as well as beta-blockers; 83.1% with oral diuretics; and 59.5% with mineralocorticoid receptor antagonists (MRAs). The usage of these therapies was higher across BSA subgroups. Creatinine, uric acid, white blood cells, and high-sensitivity C-reactive protein levels were significantly higher with the increase in BSA levels (*Table 2*).

**Table 2.** Drug treatment and laboratory blood tests during outpatient visits according to body surface area (m<sup>2</sup>)

	All (n = 9104)	<1.78 (n = 2226)	1.78–2.07 (n = 4652)	>2.07 (n = 2226)	P-value
<b>Drug treatment</b>					
ACE inhibitors/ARBs	8061/9093 (88.7%)	1836/2224 (82.6%)	4141/4644 (89.2%)	2084/2225 (93.7%)	<0.001
Beta-blockers	8057/9101 (88.5%)	1885/2225 (84.7%)	4125/4650 (88.7%)	2047/2226 (92.0%)	<0.001
MRAs	5414/9101 (59.5%)	1270/2225 (57.1%)	2766/4650 (59.5%)	1378/2226 (61.9%)	0.005
Diuretics, oral	7559/9100 (83.1%)	1823/2224 (82.0%)	3855/4650 (82.9%)	1881/2226 (84.5%)	0.072
Digitalis	2106/9098 (23.2%)	511/2225 (23.0%)	1061/4647 (22.8%)	534/2226 (24.0%)	0.552
Statins	5519/9100 (60.7%)	1188/2225 (53.4%)	2931/4649 (63.1%)	1400/2226 (62.9%)	<0.001
Antiplatelets	4480/9100 (49.2%)	1003/2225 (45.1%)	2403/4649 (51.7%)	1074/2226 (48.3%)	<0.001
Oral anticoagulant	3844/9099 (42.3%)	892/2225 (40.1%)	1951/4648 (42.0%)	1001/2226 (45.0%)	0.004
Amiodarone	1276/9099 (14.0%)	275/2225 (12.4%)	644/4648 (13.9%)	357/2226 (16.0%)	0.002
Ivabradine	763/9099 (8.4%)	203/2225 (9.1%)	370/4648 (8.0%)	190/2226 (8.5%)	0.255
Nitrates	1763/9098 (19.4%)	400/2224 (18.0%)	954/4648 (20.5%)	409/2226 (18.4%)	0.017
Calcium channel blockers	1039/9098 (11.4%)	191/2225 (8.6%)	549/4648 (11.8%)	299/2225 (13.4%)	<0.001
<b>Laboratory blood tests</b>					
WBC (cells/ $\mu$ L)	7613.6 $\pm$ 6098.4	7581.6 $\pm$ 10360.2	7539.7 $\pm$ 4312.0	7799.5 $\pm$ 2152.5	<0.001
Creatinine (mg/dL)	1.29 $\pm$ 2.30	1.23 $\pm$ 0.92	1.28 $\pm$ 1.91	1.36 $\pm$ 3.63	<0.001
Uric acid (mg/dL)	6.86 $\pm$ 2.79	6.46 $\pm$ 3.04	6.90 $\pm$ 2.90	7.17 $\pm$ 2.19	<0.001
Total cholesterol (mg/dL)	167.94 $\pm$ 45.1	172.12 $\pm$ 45.82	166.40 $\pm$ 44.23	167.10 $\pm$ 45.93	<0.001
Sodium (mmol/L)	139.37 $\pm$ 3.76	139.17 $\pm$ 3.91	139.44 $\pm$ 3.72	139.45 $\pm$ 3.66	0.131
Potassium (mmol/L)	4.46 $\pm$ 0.53	4.47 $\pm$ 0.55	4.47 $\pm$ 0.52	4.42 $\pm$ 0.52	0.004
hsCRP (mg/L)	7.14 $\pm$ 12.74	6.28 $\pm$ 11.12	6.66 $\pm$ 12.20	8.84 $\pm$ 14.87	<0.001
Bilirubin (mg/dL)	0.87 $\pm$ 0.84	0.85 $\pm$ 0.64	0.86 $\pm$ 1.01	0.90 $\pm$ 0.59	0.027

BSA, body surface area; hsCRP, high-sensitivity C-reactive protein; MRA, mineralocorticoid receptor antagonist; WBC, white blood cells.

### *Follow-up outcomes*

Data regarding mortality during 1-year follow-up were available in 8875 patients (97.5% of the study cohort). Out of this population, 718 (8.1%) patients have died. An inverse relationship between all-cause mortality and BSA subgroups was observed: highest in the low BSA quartile (11.4%), lower mortality in the Q1–Q3 quartiles (7.6%), and lowest in the uppermost BSA quartile (5.7%),  $P < 0.001$  (Table 3). Cardiovascular death was determined in 371 patients (4.2% of the study cohort) and was inversely associated with BSA subgroup distribution ( $P < 0.001$ ). Recurrent HF hospitalizations during 1-year follow-up were documented in 1029 of 8316 patients (12.4%), and were not significantly different between BSA subgroups ( $P = 0.392$ ).

**Table 3.** One-year outcomes according to body surface area subtypes (m<sup>2</sup>)

	All (n = 9104)	<1.78 (n = 2226)	1.78–2.07 (n = 4652)	>2.07 (n = 2226)	P-value
All causes of death	718/8875 (8.1%)	247/2165 (11.4%)	347/4541 (7.6%)	124/2169 (5.7%)	<0.001
CV death	371/8875 (4.2%)	131/2165 (6.1%)	178/4541 (3.9%)	62/2169 (2.8%)	<0.001
Non-CV death	162/8875 (1.8%)	59/2165 (2.7%)	75/4541 (1.6%)	28/2169 (1.3%)	<0.001
Unknown	185/8875 (2.1%)	57/2165 (2.6%)	94/4541 (2.1%)	34/2169 (1.6%)	0.049
HF hospitalization	1029/8316 (12.4%)	263/2049 (12.8%)	506/4255 (11.9%)	260/2012 (12.9%)	0.392

BSA, body surface area; CV, cardiovascular; HF, heart failure.

### *Predictors of all-cause mortality*

Multivariable analysis was performed by Cox regression analysis to identify independent predictors for all causes of 1-year mortality. Multiple variables including baseline characteristics, co-morbidities, and drug therapies were significantly and independently associated with mortality, as shown in *Table 4*. Other than severely reduced functional class (NYHA III–IV) (HR 2.152, 95% CI 1.822–2.541), the lowest BSA quartile (BSA <1.78 m<sup>2</sup>) was the strongest predictor of 1-year mortality compared with the highest quartile (BSA >2.07 m<sup>2</sup>) in the multivariate model (HR 1.823, 95% CI 1.398–2.376).

**Table 4.** Multivariable predictors for all causes of 1-year mortality

Variable	Multivariable analysis	
	HR (95% CI)	P-value
BSA < Q1 <sup>a</sup>	1.823 (1.398–2.376)	<0.0001
BSA Q1–Q3 <sup>a</sup>	1.255 (1.000–1.576)	0.0503
Female gender <sup>b</sup>	0.657 (0.534–0.808)	<0.0001
Age (years)	1.026 (1.018–1.034)	<0.0001
Systolic BP (mmHg)	0.985 (0.981–0.989)	<0.0001
LVEF <45% <sup>c</sup>	1.387 (1.108–1.736)	0.0042
NYHA III–IV	2.152 (1.822–2.541)	<0.0001
S3 gallop	1.374 (1.042–1.813)	0.0245
Mitral regurgitation	1.223 (1.033–1.448)	0.0193
Aortic stenosis	1.531 (1.140–2.055)	0.0047
Atrial fibrillation	1.332 (1.129–1.572)	0.0007
Diabetes mellitus	1.403 (1.188–1.657)	<0.0001
Peripheral vascular disease	1.463 (1.197–1.789)	0.0002
Chronic kidney dysfunction	1.628 (1.366–1.940)	<0.0001
Hepatic dysfunction	1.342 (0.983–1.831)	0.0642
Depression	1.411 (1.104–1.804)	0.0059
ACE inhibitor and/or ARB	0.756 (0.615–0.929)	0.0079
Beta-blockers	0.653 (0.527–0.810)	0.0001

BP, blood pressure; BSA, body surface area; CI, confidence interval; HR, hazard ratio; Q, quartile.

<sup>a</sup> Reference value BSA > Q3.

<sup>b</sup> Reference value male.

<sup>c</sup> Reference value LVEF ≥45%

Table 5 shows the HR for 1-year mortality according to BSA levels. In addition to the unadjusted model, data are presented after full adjustment for all significant covariates, and separately after adjustment for age and gender, the most significant parameters influencing BSA. BSA displayed a significant, stepwise, inverse relationship with all-cause mortality in all models, including after comprehensive adjustment for confounders. The HR for 1-year mortality was 1.823 (95% CI 1.398–2.376) for the lowest quartile of BSA  $<1.78 \text{ m}^2$  and 1.255 (95% CI 1.000–1.576) for the Q1–Q3 quartiles ( $1.78 < \text{BSA} < 2.07 \text{ m}^2$ ), compared with the highest quartile ( $\text{BSA} > 2.07 \text{ m}^2$ ). Moreover, entering BSA as a continuous variable showed similar results, with an adjusted HR of 0.908 (95% CI 0.870–0.948) for each increase of  $0.1 \text{ m}^2$  in BSA levels (Table 5).

**Table 5.** Hazard ratios for 1-year mortality according to body surface area

Comparison	Unadjusted HR (95% CI)	HR adjusted for age and gender (95% CI)	HR adjusted for all <sup>a</sup> (95% CI)
BSA < Q1 vs. Q1–Q3	1.529 (1.299–1.800), $P < 0.001$	1.710 (1.438–2.033), $P < 0.001$	1.452 (1.197–1.760), $P < 0.001$
BSA < Q1 vs. >Q3	2.073 (1.670–2.572), $P < 0.001$	2.156 (1.709–2.721), $P < 0.001$	1.823 (1.398–2.376), $P < 0.001$
BSA Q1–Q3 vs. >Q3	1.355 (1.104–1.664), $P = 0.004$	1.261 (1.024–1.553), $P = 0.029$	1.255 (1.000–1.576), $P = 0.050$
BSA continuous (unit = 0.1)	0.888 (0.859–0.918), $P < 0.001$	0.871 (0.838–0.905), $P < 0.001$	0.908 (0.870–0.948), $P < 0.001$

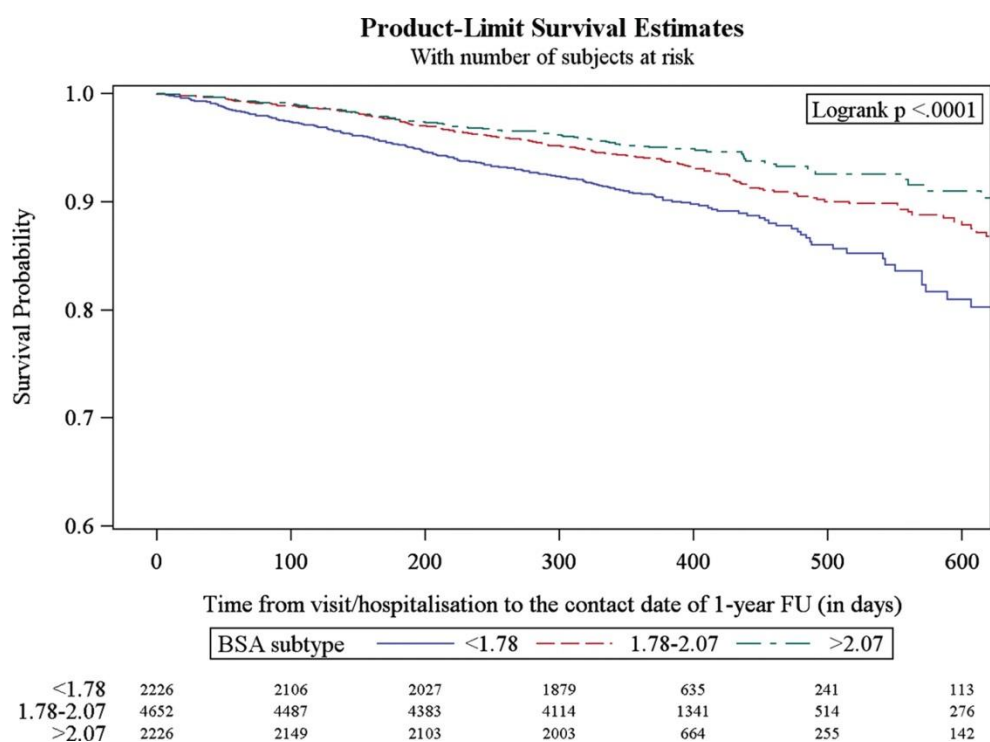
Comparison between BSA quartiles or as a continuous variable, for each increase of  $0.1 \text{ m}^2$ .

BSA, body surface area; CI, confidence interval; HR, hazard ratio; Q, quartile.

<sup>a</sup> See Table 4.

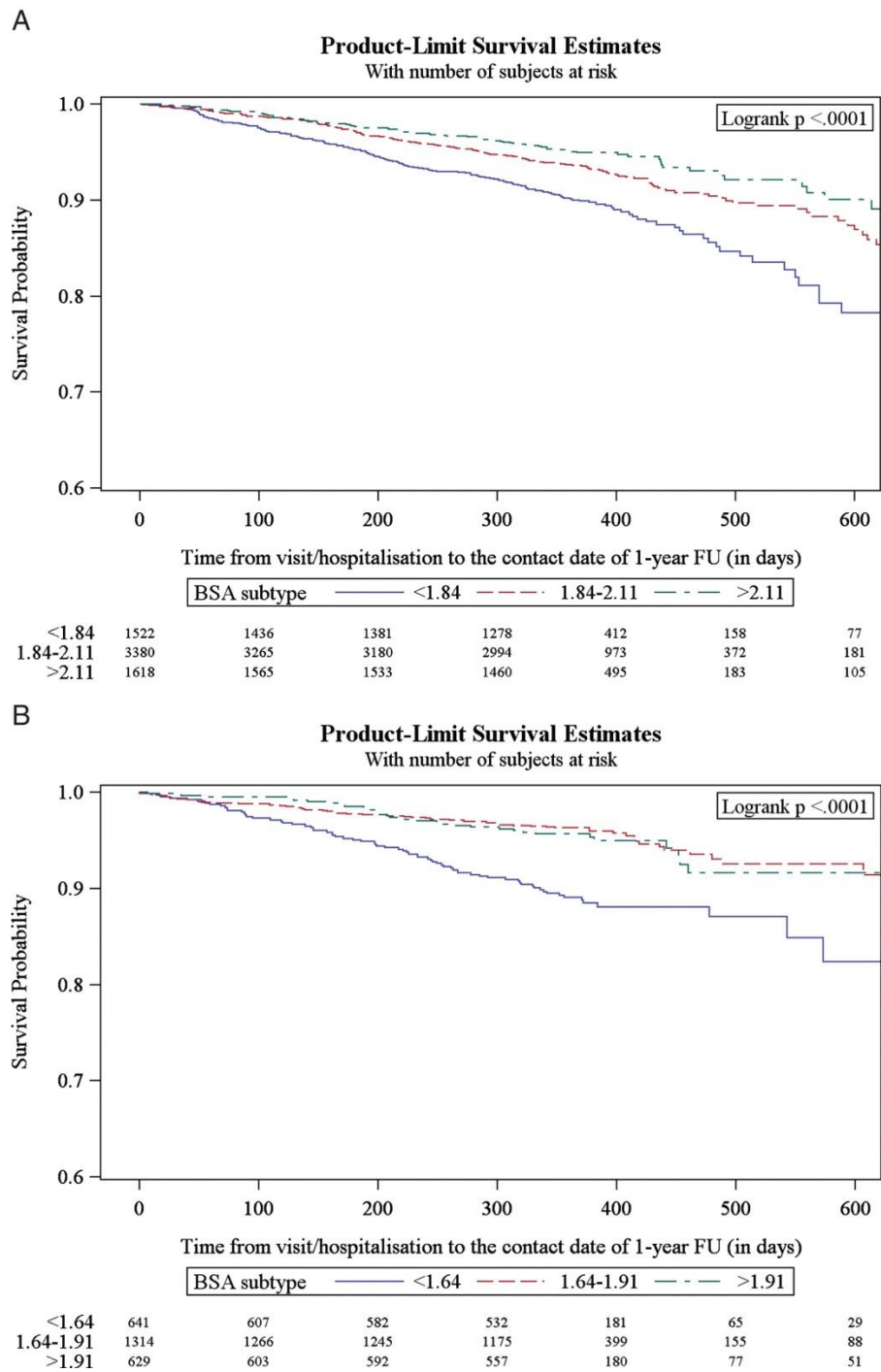
The lowest BSA quartile was significantly associated with 1-year mortality in both patients with preserved ( $\geq 45\%$ ) and reduced ( $< 45\%$ ) LVEF (adjusted HR 2.048, 95% CI 1.045–4.013,  $P = 0.03$ , and 1.804, 95% CI 1.351–2.408,  $P < 0.001$  compared with the highest BSA quartile, respectively).

Kaplan–Meier survival curves for all causes of death, stratified by BSA subgroups, are presented in Figure 1, showing the continuation of the graded inverse relationship between BSA subgroups and mortality also beyond the first year of follow-up (log-rank  $P < 0.0001$ ). Because BSA is inherently influenced by gender, we additionally performed separate survival analysis according to BSA quartiles of each gender (Figure 2). In both genders, subjects with the lowest BSA quartile (males  $< 1.84 \text{ m}^2$  and females  $< 1.64 \text{ m}^2$ ) had significantly higher mortality rates (log-rank  $P < 0.0001$  for both genders). However, the stepwise association with mortality was more distinct in males.



**Figure 1.** Kaplan–Meier curves for all causes of death by body surface area (BSA) subtypes. FU, follow-up.





**Figure 2.** Kaplan–Meier curves for all causes of death by body surface area (BSA) subtypes, separately for (A) males and (B) females. FU, follow-up.

## Discussion

The results of the present study indicate that BSA, a common measure of body size used for indexing physiological parameters, is inversely and progressively associated with all-cause and cardiovascular mortality, but not HF hospitalizations, in a large cohort of chronic HF patients. This relationship, coinciding with the 'obesity paradox', was noted even after significant adjustment for confounders, including age and gender.

The phenomenon of the obesity paradox was repeatedly demonstrated in studies analysing cohorts of both acute and chronic HF patients.<sup>2-8, 25</sup> This was documented even though obesity is a well-established risk factor for HF.<sup>1</sup> The main mechanism proposed for the obesity paradox in HF is the greater metabolic reserve existing in obese HF patients, in contrast to the catabolic and inflammatory changes leading to cardiac cachexia.<sup>26</sup> However, other contributing factors were suggested, including lower sympathetic activation and earlier presentation of symptoms in the obese HF patients, and confounding factors such as age and gender, which may bias the results.<sup>14-18, 27</sup>

The majority of studies analysing adiposity in HF identified obesity by measuring BMI. However, the accuracy and reliability of this method in defining obesity and correcting weight for height was questioned.<sup>13, 20</sup> BSA correlates more closely to physiological parameters than body weight. Different formulae that estimate whole BSA were developed over the years.<sup>24, 28</sup> The DuBois brothers were the first researchers (in 1915) to develop an equation incorporating both mass and height, based on data from nine cadavers.<sup>29</sup> Years later, Mosteller suggested a simplified approximation to this formula in a letter published in 1987 in the *New England Journal of Medicine*.<sup>23</sup> This simplified equation [ $BSA = (\text{weight (kg)} \times \text{height (cm)})/3600^{1/2}$ ] has been widely adopted over the years due to its ease of calculation.<sup>28</sup> Verbraecken and colleagues found a close agreement between Mosteller's equation and BSA values obtained with traditional complex methods, recommending that this formula deserves to be used as the first choice for BSA calculation in clinical research and practice.<sup>24</sup> Importantly, they demonstrated the accuracy and applicability of the Mosteller equation not only in normal weight, but also in overweight and obese adults.

Although BSA is commonly used in medicine as a biometric unit to adjust size, mass, and volume, its clinical significance as an outcome predictor in cardiovascular diseases was scantily investigated. A small BSA was found to be an independent negative outcome predictor after coronary artery bypass surgery.<sup>30</sup> An additional study found that adult candidates for heart transplantation with lower BSA, including most female patients, had worse prognosis.<sup>31</sup> Moreover, specifically in chronic HF, Futter and colleagues found in a cohort of 2271 patients that BSA was a stronger predictor of mortality than other measures of body habitus including BMI, concluding that the greater the overall bulk of the body the better the survival.<sup>20</sup> The current study results are in concordance with these observations, demonstrating an inverse relationship between BSA and mortality in chronic HF patients, establishing low BSA as one of the strongest independent predictors of 1-year mortality. The inverse relationship with mortality was stepwise, with a borderline prognostic significance of the middle vs. high BSA subgroup in the multivariate analysis.

The lack of association between BSA and HF hospitalization rates observed in the current study was similarly shown in a recent meta-analysis investigating the relationship of BMI and outcomes in patients with chronic HF.<sup>8</sup> In both studies, a U-shaped association with rehospitalizations was demonstrated, which was distinct from the inverse relationship which was seen with mortality.

In contrast to BMI, there are consistently and significantly higher BSA values in males than in females, both in normal weight and in overweight and obese subjects. The commonly accepted 50th percentiles for BSA are 1.94 m<sup>2</sup> for adult men and 1.69 m<sup>2</sup> for adult women.<sup>24</sup> As expected, this observation was also noted in the present study, in which the gender distribution varied significantly across BSA quartiles. Therefore, we have adjusted the HRs of mortality for age and gender in a separate model, and analysed survival curves according to the BSA quartiles of each gender individually. The obesity paradox was demonstrated in both genders; however, there was a stronger inverse association

between BSA and mortality in males compared with females. This finding could be partly due to the significantly higher mortality rates observed in males than in females in our HF cohort.

### *Limitations*

The current study is based on an observational multicentre registry of HF patients. Some important limitations of this registry are acknowledged elsewhere.<sup>22</sup> Additional co-morbidities and cardiovascular risk factors influencing HF progression and outcomes may not have been evaluated in the ESC HF registry and therefore may account for residual confounding effects which were not adjusted for in the present study. Moreover, we have not used statistical methods such as propensity score analysis for matching imbalances in baseline characteristics and disease severity between BSA subgroups. ç

Body surface area was estimated based on a commonly used formula and not on actual BSA measurements using methods such as three-dimensional whole-body scanning. In addition, several studies have pointed out that BSA calculation is less accurate in severely obese subjects, which may have influenced the results. Moreover, we have not compared the predictive ability of BSA with BMI, the more commonly investigated parameter in studies analysing the obesity paradox in HF, nor have we evaluated whether BSA is linked to differences in body fat distribution. These important questions should be addressed in future studies.

### **Conclusions**

Body surface area is a strong independent predictor of mortality in chronic HF subjects. Similar to other measures of body habitus, the obesity paradox is observed in HF using Mosteller's formula for BSA estimation. Since BSA is routinely calculated for indexing physiological parameters in the cardiovascular field, it may serve as an important and practicable prognostic indicator for adverse outcomes in chronic HF patients.

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## Appendix

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